GlaxoWellcome

August 30, 1999

Management Dockets
Dockets Management Branch
Food and Drug Administration
HFA-305, Room l-23
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket Number 99D-1454
Comments on Draft Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products

Dear Sir or Madam:

GlaxoWellcome endorses the publication of this Draft Guidance for Industry and commends the Inhalation Drug Products Working Group of the Chemistry, Manufacturing and Controls Coordinating Committee for providing a comprehensive document for review.

We appreciate the opportunity to provide input on the Draft Guidance and offer the enclosed comments and recommendations in an effort to assist the Agency in producing a final guidance that will provide sponsors with a thorough, yet flexible approach to the development and registration of these important dosage forms. Our comments are divided into two sections: general comments applicable to the entire document and specific comments identified by line number.

We fully support this effort and commend the Agency for its continued commitment to improving the quality of these important medicines. In addition, we endorse the comments submitted on the Draft Guidance by the International Pharmaceutical Aerosol Consortium, of which GlaxoWellcome is a member. Please contact me at 919-483-5121 if you require clarification of any of these comments.

Sincerely,

Lorna C. Wilson

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Project Director
Regulatory Affairs

99D-1454

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Comments on the Draft Guidance for Industry
Nasal Spray and Inhalation Solution, Suspensions, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation
(Docket No. 99D-1454)

GENERAL COMMENTS

1. **Alternative Approaches:** We strongly agree with the Agency's policy, as documented in MAPP 4000.2 "Developing and Issuing Guidance for Industry", that requires a statement in all guidance documents that the guidance "does not impose mandatory requirements" and that "An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both." However, in addition to the required statement regarding the non-binding nature of guidance documents, we note that MAPP 4000.2 also states that

   > "If an employee wishes to request that a sponsor use an alternative approach, this decision should be discussed first with his or her supervisor and then with the office or division director as appropriate. Similarly, alternative approaches proposed by sponsors may be acceptable and should be discussed with CDER supervisors before they are accepted. **The decision to deviate from a guidance document should be clearly documented."**

   We fully endorse documenting discussions and decisions regarding alternative approaches. However, the wording in the MAPP does not distinguish between significant and insignificant departures as Guidance documents do. This might be interpreted as implying that all alternative approaches may need to be discussed with the appropriate Division prior to implementation. We request that the Agency clarify the intent with regard to discussing alternative approaches and revise the wording in MAPP 4000.2 and this Draft Guidance to provide reviewers and sponsors with a clear understanding of the policy.

2. **Global Harmonization:** There are several areas in the Guidance that are inconsistent or silent with regard to ICH guidelines and compendia1 harmonization. In keeping with the Agency's commitment to global harmonization, we request the Agency incorporate language into the Guidance to reflect the principles and key elements of the following harmonized areas:

   - ICH Q1 A *Stability Testing of New Drug Substances and Products* supports limited extrapolation of real time stability data to establish the expiration-dating period.
   - The ICH Q1A provision for using bracketing and matrixing concepts, if justified, in stability protocols.
   - The ICH Q3B philosophy that only degradants and not synthetic impurities need to be monitored in drug products.
   - The use of non-stability indicating methods, where appropriate as per ICH Q6A.

3. **Specifications:** The Guidance defines a detailed specification for Content Uniformity that is consistent with the specification published in the Draft Guidance for MDIs and DPIs. As stated in our comments on the MDI and DPI guidance, it would be more useful for the Draft Guidance to provide the Agency's current thinking or philosophy on acceptable approaches to setting specifications, including discussion of acceptable empirical or statistical methods.

   For example, the ICH philosophy of setting specifications as stated in the *Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (62 FR 62890, 62891 – 62892) is one example of a basis from which meaningful specifications can be derived. The draft ICH Guideline states:

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development upon which specifications are based, adherence to good manufacturing practices (GMPs) and a validated manufacturing process, e.g., raw material testing, in-process testing, stability testing.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

When a specification is first proposed justification should be presented for each procedure and each acceptance criterion included. The justtjkation should refer to relevant development data, pharmacopeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate. Additionally a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

This philosophy, or something similar, should be incorporated into the Draft Guidance as a guiding principle for establishing appropriate specifications for these dosage forms. As each new product development is unique, we think it is important to provide a framework for evaluating a product, rather than a detailed specification. For this reason, we do not agree that one specification, such as that proposed by the Agency for content uniformity, should apply to each and every product.

4. **Differentiating Between Development, Product Characterization, and Routine Quality Control Tests:** A key concern is that the Draft Guidance does not acknowledge the difference between development data, product characterization data and ongoing data generation for routine quality control purposes. We agree ongoing controls should be carefully selected to provide a battery of tests which combine to assure that the required product characteristics and standards have been achieved for each lot produced. However, extensive testing which confirms what is already assured from development, validation, control of incoming materials or during manufacture is excessive and does not increase assurance of product quality.

   Throughout this Draft Guidance, this distinction is not clear. As an example, the Draft Guidance recommends the acceptance criteria for pumps include pump delivery, particle/droplet size distribution, leachables and spray pattern, but also lists each of these as finished product specification tests. It is unnecessary to control these at both the component and the finished drug product stages. In addition, there are places in the Guidance where excessive testing is recommended within the same stage. For example, the Guidance calls for application of a specification for pump delivery as well as a test for spray content uniformity for release of the finished product. The test for pump delivery is unnecessary and does not provide increased assurance of quality as the test for spray content uniformity through life directly evaluates the performance of the product.

   We agree that it is important to consider the appropriateness of each of the tests for use in the development, characterization or control of these products. However, we suggest the Guidance incorporate wording to acknowledge that the selection of the appropriate tests should be on a product-specific basis. It is understood that a sponsor would be required to provide a sound scientific justification for each particular development, characterization and quality control program.

Finally, the Guidance also requires that extensive data be developed to characterize the product on the first three commercial batches. We agree that during development the key characteristics of a product should be thoroughly predicted and targeted. However, characteristics may then be confirmed as part of the validation process or the pre-validation scale-up work, making it unnecessary to repeat product characterization testing on the first three commercial batches.

5. **Consistency with the Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action:** We recommend that a stronger link be created between tests in this guidance that are also included in the Bioavailability/Bioequivalence (BA/BE) Draft Guidance. Each guidance document should be consistent in the level of detail and the requirements, unless there are specific differences necessary for BA/BE assessments. Examples where differences currently exist include: 1) priming/repriming 2) particle size distribution by Cascade Impaction 3) profiling of sprays near container exhaustion and 4) spray pattern.

SPECIFIC COMMENTS

Section/Topic	Line Number(s)	Comments
I. INTRODUCTION	3 - 6	We strongly support application of the same standards to ANDAs and NDAs, as product quality considerations are independent of the regulatory mechanism for approval. We suggest addition of a statement to indicate that the Guidance is not intended to be applied to approved drug products.
II. BACKGROUND		
A. Nasal Sprays	37-38	The term "metering" suggests that all pumps act as metering devices. This is not strictly true in the case of a unit dose pump. We suggest the following alternative wording may be more appropriate, ". . .in non-pressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose may be metered by the spray pump or pre-dispensed."
	41	We suggest that the parenthetical statement (typically in microgram quantities) is not representative of all nasal spray products and should be omitted.
	63 - 66	This section should be revised as follows (new text underlined): "The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays depending on the intended site and mode of action. The doses administered may be so small that blood or serum concentrations are generally undetectable by routine analytical procedures. Even where the pharmacokinetics of nasal doses can be measured. the measurements onlv allow a crude estimate of total nasal deuosition. Moreover, bioequivalencv studies are complicated by the fact that only a portion of the dose reaches the site of action. The remainder of the dose is swallowed and absorbed through the gastrointestinal (GI) tract. Thus. even if determination of blood or serum concentrations were possible, additional and more extensive studies would be necessary to distinguish the contributions of the drug absorbed from the nasal, buccal, and GI routes. Finally, blood levels are not necessarily correlated to uharmacodvnamic effects if these drugs act locally and not systemically." In addition, this section should include reference to the draft Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

Section/Topic	Line Number(s)	Comments
B . Inhalation Solutions and Suspensions	68 - 78	We agree with the proposed rule published in the Federal Register on September 23, 1997 (Vol. 62, No. 184) which would require that ". . all aqueous-based inhalation solutions [and suspensions] for nebulization be manufactured as sterile." However, we do not agree that this should be required for non-aqueous oral inhalation spray drug products that do not support microbial growth.
III. DRUG PRODUCT		
C. Specifications for the Formulation Components		
1. Active Ingredient(s)	167-212	The current positioning of the discussion on active ingredient(s) in this Draft Guidance is inconsistent with the organization of applications, that is, Part I Drug Substance and Part II Drug Product. This may detract from the importance of Part I and serve to dilute the advice on what information should be submitted. It is recommended that the Guidance be revised to include a separate section on drug substance which would refer to the appropriate guidance documents and comment on the additional information that should be considered for drug substances formulated in these dosage forms.
	185 - 188	This sentence should be revised as follows: "For suspension formulations, the specification submitted in the application should include controls for particle size distribution and physical properties (e.g., shape, crystal habit, morphology and rugosity). . . "
	193-195	Controls on amorphous content of micronized drug should be considered if it has been demonstrated during development studies that this is critical to the stability of the product.
	201 - 203	It is recommended that the sentence "Any recurring impurity found in the drug substance at a concentration of 0.1 percent or greater, relative to the parent drug substance, should be identified and qualified." be replaced with a cross-reference to ICH guidelines Q3A Impurities in New Drug Substances and Q3C Impurities: Residual Solvents to acknowledge the Agency's adoption of these guidelines and to ensure the consideration of the maximum daily dose in determining the appropriate qualification threshold.

Section/Topic	Line Number(s)	Comments
1. Active Ingredient(s) (cont.)	203 - 206	It is requested that guidance be provided on how acceptance criteria for impurities should be justified. We believe this could be through the use of tolerance intervals, process capability (>3 sigma) or the use of empirical methods from data collected on the relevant batches.
2. Excipients	234 - 237	The first sentence should be revised to read "For noncompendial excipients, adequate DMFs with appropriate authorization or an equivalent package of information.. . " to clarify that sponsors may choose to submit the information directly in the application.
	239 - 243	The requirement to supplement the USP/NF monograph tests with additional controls should not be routine. The need for additional controls should be assessed on a case-by-case basis during the development of the product. If there were additional controls that should be routinely applied, we would support the development of USP monographs for inhalation grade excipients.
	256 - 263	There appears to be a significant additional burden on the applicant regarding the testing of excipients that are to be accepted on certificate on analysis. Supply agreements exist between the applicant and the excipient manufacturers and as part of GMP, suppliers are subjected to regular audits. Provided an adequate number of batches are tested by the applicant before submission, testing batches post-approval is unnecessary. Furthermore the final sentence appears to be repetition of the earlier points, if the number of batches before submission were adequate, multiple incoming batches will have been tested.
D. Manufacturers	286	The Draft Guidance recommends that sponsors include the Central File Number (CFN) for each facility. We request this be changed to the Establishment Registration Number or Labeler Code because sponsors do not have direct access to CFNs. Alternatively, the Agency could publish CFNs on the inter-net.
	292 - 293	We suggest that the requirement to identify the name and address for excipient manufacturers should be clarified, consistent with lines 227 – 229, to indicate that this is only required "for excipients that may have a direct impact on the performance of the drug product."

Section/Topic	Line Number(s)	Comments
E. Method(s) of Manufacture and Packaging	**300 - 302**	As written this sentence may cause confusion, we request that it be made clear that nasal sprays are not required to be sterile.
	304 - 307	We agree that the micronization process should be fully validated and that operating parameters should be appropriately specified in the batch record. However, we suggest that the key information to be submitted in the NDA should be the required particle size profile and that inclusion of extensive processing parameters in the NDA may prohibit adjustments to maintain this profile. The adequacy of the validation and specified control parameters to assure the required particle size profile is best assessed during inspection.
	317	Following the sentence which ends "…controls record should be submitted." please insert the following sentence "If the master batch production record is not finalized at the time of submission, this may be provided post-approval."
	320 - 323	The sentence "The manufacturing directions.. .of the drug product." should be deleted as this is a requirement of the GMP regulations.
	327 - 328	We suggest deleting osmolality and viscosity as suggested in-process tests. These can be adequately characterized during development and controlled during commercial manufacture through the application of GMPs.

Section/Topic	Line Number(s)	Comments
F. Specifications for the Drug Product	**349 - 807**	The terminology in this section is confusing in two respects, 1) inclusion of information covering a wide spectrum, that is, release testing, stability testing, component testing and development studies and 2) use of different terminology, such as, acceptance criteria, stability specification and release specification. We suggest this section focus on Regulatory specifications for the finished product and use consistent terminology when referring to specifications.
1. Nasal Sprays		
a. Appearance, color and clarity	**370 - 378**	The requirement for a quantitative test and appropriate acceptance criteria for color of the formulation is appropriate if there is a color change on storage. In cases where color is associated with the formulation, but it has been demonstrated that it does not change over time, a regulatory specification should not be necessary.
b. Identification	**385 - 386**	The requirement that the identity test should be specific for the single enantiomer should be waived if adequate data are presented to demonstrate that the enantiomeric form is maintained throughout the manufacturing process.
c. Drug Content (Assay)	**388 - 397**	The drug content assay does not provide increased assurance of quality as the test for spray content uniformity through life directly evaluates the performance of the product making this test redundant. It does, however, have value during product development, process validation and may be appropriate as an in-process control. As an in-process control it is unnecessary for this assay to be stability indicating. We note that ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances allows the use of non-stability indicating methods, if appropriately justified. Typically, the amount of drug substance loaded onto the HPLC column in the assay method will be much less than that used in the stability-indicating impurities method, hence the-impurities would likely be undetected.

Section/Topic	Line Number(s)	Comments
c. Drug Content (Assay) (cont.)	391 - 392 395 - 396 397	If this section is retained in the final Guidance, then it is suggested that the following be deleted as these statements do not provide any additional useful information to sponsors. "This test provides assurance of consistent manufacturing (e.g. formulation, filling, sealing)." "adherence of the drug substance to the container and closure components" and "and/or leakage"
d. Impurities and Degradation Products	399 - 408	We recommend adding a reference to ICH Q3B Impurities in New Drug Products and including the following statement from the guideline to clarify that "Impurities present in the new drug substance need not be monitored in drug products unless they are also degradation products."
e. Preservatives and Stabilizing Excipients Assay	410-415	We suggest the following statement in lines 630-632 also applies to assay of these ingredients in nasal sprays. "In addition, for a semi permeable container closure system, the potential for offsetting assay loss from degradation with apparent assay gain from evaporative effects should be considered"
f. Pump Delivery	417 - 426	We agree that the pump manufacturer is responsible for the performance of the pump and this is reflected in the inclusion of performance tests in the release specification for the pumps in Section G line 889. We also support verification of pump spray weight by the applicant during development studies and as an acceptance test on the incoming components as it is a contributing factor to the delivery performance of the product. However, it should not be required as a specification test for the product, since the critical performance parameter is the spray content which is controlled in the drug product specification by acceptance limits based on the label claim. We also recommend that the limits on the capability of the pump be defined on a case-by-case basis.

Section/Topic	Line Number(s)	Comments
g. Spray Content Uniformity h. Spray Content Uniformity Through Container Life	428 - 489	As with all other specifications, the Spray Content Uniformity specification should be established on a product-specific basis taking into consideration the development data, pharmacopeial standards, data on preclinical and clinical batches, results from stability studies and an assessment of the implications on safety and efficacy. The final specification should also allow for expected variations in the components, manufacturing process and analytical test procedures. We recommend that the Guidance be revised to delete the specifications proposed for Content Uniformity and that this section be reworded to describe the general approach that should be followed in arriving at an appropriate Content Uniformity specification. We also request the Agency include guidance on retesting, as the current expectation that no values should occur outside a given range is very restrictive. Normal statistical theory predicts out of specification results are possible, although improbable. These results, when they do occur, are difficult to investigate and repeat analyses are not easily allowed under the Barr decision. The Draft Guidance describes two types of tests to assess both inter- and intra-container spray content uniformity. We recommend the Guidance allow alternative approaches to how the test is performed, for example, combining the attributes of the tests under g. and h., provided adequate assessment of both inter- and intra-container content uniformity are performed.
	430 - 432	We recommend the initial statement is expanded to account for unit dose sprays and it is clarified that the reference to "among batches of drug product" refers to development studies, as tests on several batches are not required to confirm that individual batches are acceptable. For example, "The spray discharged from the nosepiece should be thoroughly analyzed for the drug substance content of multiple sprays from an individual container (unless single dose) and among containers. During development studies a number of batches of drug product using different batches of input pack components should be assessed."
	435 - 437	We suggest that the number of actuations included in a determination of dose content uniformity be equal to the number of actuations required to administer the usual recommended dose as described in the product labeling and not restricted to the minimum dose per nostril.

Section/Topic	Line Number(s)	Comments
g. Spray Content Uniformity (cont.)	438	We recommend that actuation should be performed either manually following the patient instructions or automatically using defined actuation parameters (e.g. stroke length, depression force, **speed, hold and return times)** that have been demonstrated to give equivalent performance to manual actuation.
h. Spray Content Uniformity Through Container Life (cont.)	444	At present the advice on number of containers (10 recommended on line 444 and in acceptance criteria) seems to be inconsistent with the recommendation to test multiple sprays from an individual container (line 43 1).
	456	The second tier of testing uses a further 20 containers, for multi-dose containers it may be more appropriate to test a further 20 doses from the original 10 containers.
	470	The Through Container Life test recommends 5 containers while the Draft Guidance on MDIs and DPIs recommended 3 containers. It would be helpful if the Guidance provided the reason for this difference. We believe it is sufficient to test one container through use if a separate spray content uniformity test is used to confirm the uniformity between containers.
i. Spray Pattern and Plume Geometry	491 - 517	Spray pattern and plume geometry in an unconstrained environment are indirect measures of reproducibility of dosing. This is determined directly by the spray content uniformity test. While spray pattern and plume geometry are recognized as useful in the control of pumps at the component stage, they provide little further control over product quality. While we agree that spray pattern and plume geometry should be evaluated with the formulation during pump selection, we do not agree that a regulatory specification for spray pattern is necessary. The factors affecting spray pattern and plume geometry such as pump and nozzle design and the critical dimensions of orifice diameter are better controlled through acceptance criteria applied to the pump and nozzle at the component stage. We recommend deleting this section of the Guidance, as the proposed controls on the pump and nozzle combined with other drug product performance tests provide adequate control over product quality.

Section/Topic	Line Number(s)	Comments
i. Spray Pattern and Plume Geometry (cont.)	491 - 517 (cont.)	If a specification for spray pattern is retained in the final guidance, we recommend the following revisions: • Delete the requirement to specify the shape of the spray pattern, as it is not relevant to implement a specification for description of the spray image (e.g. ellipsoid), when there are two other defined parameters (axis and ratio) which accurately define the spray image. There is no benefit to product quality by introducing a general description, which is open to subjective interpretation, especially since the test is not conducted in a manner truly representative of the *in vivo* use of the product. • The requirement to test at two different distances should not be necessary, provided multiple distances were evaluated during method development to determine the optimal distance to obtain a spray pattern that is of uniform density and reproducible.
j. Droplet Size Distribution	519 - 528	While we support the full characterization of droplet size during development, the requirement for a 3 or 4-point drug product specification for an intranasal formulation is not understood. We would agree that very small droplets have the potential to be inhaled rather than deposited on the nasal mucosa, so a limit on these small particles should be considered. However, most spray pumps are not designed to generate sufficient force to create droplets in the respirable range. If it can be demonstrated that the pump does not generate these, a test and limit for potentially respirable droplets would be unnecessary. If a test and limit are deemed appropriate, these should be applied at the component acceptance stage rather than on the final product.
k. Particle Size Distribution (Suspensions)	530 - 538	Particle size distribution should be evaluated as part of the development stability studies. If it is shown to be stable there is no need to include it in the finished product specifications.

Section/Topic	Line Number(s)	Comments
m. Foreign Particulates	553 - 559	A specification for control of foreign particulates should only be required if it is demonstrated during development that it is appropriate. As a general rule, this should not be routinely necessary, as compliance with GMPs should provide adequate control. The statement ". . .and, in particular, from the container and closure components." implies that there is a special problem with the container closure system. However, no explanation is provided for this statement.
n. Microbial Limits	569 - 572	Please clarify this section to indicate that it applies only to multi-dose nasal sprays which support microbial growth and not to unit dose nasal sprays.
0. Preservative Effectiveness	575 - 582	The requirement to establish a specification for preservative effectiveness in addition to a specification for preservative content is redundant and provides no added assurance of product quality. While it is recognized that ICHQ6A does not apply to intranasal products, the approach to the control of antimicrobial preservative effectiveness in Section 3.3.2.2(d) would be appropriate for the control of intranasal products. ICHQ6A states: "For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content may be appropriate. These criteria should be based on the levels necessary to maintain microbiological product quality throughout the shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopeial antimicrobial preservative effectiveness test. Release testing for antimicrobial preservative content should normally be performed. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. Antimicrobial preservative effectiveness should be demonstrated during development, during scale-up, and throughout the shelf-life.. . , although chemical testing for preservative content is the attribute normally included in the specification."

Section/Topic	Line Number(s)	Comments
0. Preservative Effectiveness (cont.)		The requirement to repeat the preservative effectiveness studies on the first three production batches is unnecessary as the development studies will have established the appropriate level of preservative and the quality of the production batches will be assured through the assay for preservative content. It is suggested that preservative effectiveness be removed from the specification section and be discussed in the sections on product characterization and stability testing.
p. Net Content & Weight Loss (Stability)	584 - 593	It is appropriate to apply control over the net content for multi-dose products to ensure the labeled number of actuations through the shelf life of the product. However, this can be adequately controlled by application of in-process limits rather than through a regulatory specification at release. It is also suggested that the Guidance acknowledge that in-process fill weight measurements may be performed by alternative methods to the USP <755> (e.g. by use of tared containers) and may require different limits relating to the labeled amount plus any required overfill. Weight loss monitoring on stability may be a useful measure to understand changes in other parameters, e.g. increase in spray content or decrease in number of doses available, but it is not appropriate to set acceptance criteria for this parameter. The storage conditions and expiry period are defined to ensure acceptable product quality in terms of its critical attributes, which can be tested at any time during the product's life. Weight loss is only an indirect measure of product quality; it can only be determined relative to an initial value. It is suggested that weight loss be moved to the section on stability testing.

Section/Topic	Line Number(s)	Comments
q. Leachables (Stability)	595 - 606	We agree that leachables in the drug product should be characterized in development studies through the shelf life of the drug product or until equilibrium levels are reached. The development studies should be designed to determine the identity, if possible, concentration profile, origin of the compound and a correlation, if feasible, with the profiles of the components or raw materials. As a result of these studies, controls would then be developed and applied at the appropriate point in the component supply chain. The controls could be applied to the raw polymers, final components or at any stage in between. Alternatively, the studies may show that routine controls are unnecessary. We agree with the statement in Section G. Container and Closure Systems (lines 853 – 855) that "Such a correlation may obviate the need to evaluate leachables in the drug product formulation in future routine stability studies." and suggest that this approach be reflected in lines 597 – 606 to permit flexibility in the requirement of a specification for leachables in the drug product.
s. Osmolality	613 - 616	The relevance of applying osmolality as a finished product test is not understood as it is a characteristic of the formulation and GMP will assure the correct quantities of the ingredients. For aqueous systems we support the assessment of osmolality during formulation studies and if a solution/suspension will be hypotonic that an appropriate quantity of a tonicity agent is added to the formulation to make it isotonic. This should not be a routine test but should be determined to provide guidance to healthcare professionals and could be included on the labeling. We would agree that periodic monitoring might be appropriate (e.g., at initial and end of life for the ongoing stability programs).
2. Inhalation Solutions, Suspensions, and Sprays		
a. Appearance, Color, & Clarity	620 - 622	Refer to comments under nasal sprays.
b. Identification	624 - 626	Refer to comments under nasal sprays.

Section/Topic	Line Number(s)	Comments
c. Drug Content (Assay)	628 - 632	Refer to comments under nasal sprays. In addition, the comments relating to semi-permeable containers also apply to nasal sprays.
d. Impurities and Degradation Products	634 - 636	Refer to comments under nasal sprays.
e. Preservatives and Stabilizing Excipients Assay	638 - 641	Refer to comments under nasal sprays.
f. Sterility	643 - 646	We agree with the proposed rule published in the Federal Register on September 23, 1997 (Vol. 62, No. 184) which would require that ". . . all aqueous-based inhalation solutions [and suspensions] for nebulization be manufactured as sterile." However, we do not agree that this should be required for non-aqueous oral inhalation spray drug products that do not support microbial growth.
g. Preservative Effectiveness	648 - 650	Refer to comments under nasal sprays.
h. Foreign particulates	652 - 655	Refer to comments under nasal sprays.
j. Osmolality	661 - 663	Refer to comments under nasal sprays.
k. Net Content and Weight Loss (Stability)	665 - 667	Refer to comments under nasal sprays.
1.Leachables (Stability)	669 - 678	Refer to comments under nasal sprays. In addition, while we would agree that a development study to determine ingress of volatile compounds is appropriate, a specification applied during the ongoing stability studies should not be necessary. It is recommended that this discussion is moved to Section H. Drug Product Stability and it is made clear that this testing should only be necessary for the orimarv NDA stabilitv studies.
o. Pump Delivery for Inhalation Sprays	688 - 690	Refer to comments under nasal sprays.

Section/Topic	Line Number(s)	Comments
p. Spray Content Uniformity for Inhalation Sprays	692 - 698 700 - 701	Refer to comments under nasal sprays. The requirement to apply a separate test for the content uniformity of pre-metered dose units is unnecessary as this is an indirect measure of the spray content uniformity which is already being assessed for the finished product. Content uniformity of pre-metered dose units should be evaluated during validation of the manufacturing process.
q. Spray Content Uniformity Through Container Life for Inhalation Sprays (Device-Metered)	703 - 709	Refer to comments under nasal sprays.
r. Plume Geometry for Inhalation Sprays	711 - 733	Plume geometry in an unconstrained environment is an indirect measure of reproducibility of dosing. This is determined directly by the spray content uniformity and droplet/particle size distribution tests. These not only assay the drug, rather than measure a physical property, but the droplet/particle size distribution test is much more relevant as it includes the effect of simultaneous inhalation and constraining the plume by the throat. While we agree that plume geometry should be evaluated with the formulation during pump selection, we do not agree that a regulatory specification is necessary. The factors affecting plume geometry such as actuator design and the critical dimensions of orifice length and diameter are better controlled as part of the acceptance criteria applied to the actuators at the component stage. We recommend deleting this section of the Guidance, as the proposed controls on the actuators combined with other drug product performance tests provide adequate control over product quality.

Section/Topic	Line Number(s)	Comments
s. Particle/Droplet Size Distribution for Inhalation Sprays	*764 - 765*	The requirement to include qualification criteria for each cascade impactor in the application is unnecessary additional information that is outside the scope of the review process. This falls within current Good Manufacturing Practice under 2 l CFR 2 11.160(b)(4) and is reviewed during the pre-approval inspection. We recommend the requirement be removed from the Guidance document. If impactors of different designs were used, then we would agree that it would be appropriate to provide cross-validation data in the application.
	777 - 779	The recommendation that the total mass of drug collected on all stages and accessories should be between 85 – 115% of label claim, on a per spray basis, is inconsistent with the Stimulus to Revision for USP Chapter <601> *Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers* (Vol. 24 No. 5 Sept-Ott 1998) which requires the material balance to be not less than 75% and not more than 125%. We suggest that the USP limits for MDIs are also appropriate for these dosage forms and suggest that the Guidance be revised to adopt the USP limits to allow for the increased variability of cascade impaction testing as compared to content uniformity testing.
	785 - 787	Data will be generated during product development to demonstrate batch to batch consistency of the full particle size distribution of the emitted dose. However, for routine quality control purposes it is not appropriate to set limits that effectively define the full particle size distribution. We suggest that the full characterization of the spray be specified by determination of deposition of drug on the stages that define the fraction less than 5p.m or in the range 1 – 5 μm. Apart from that, only throat deposition should be specified.
	793 - 807	We are unaware of any circumstances that would justify the additional requirement for a second complementary test for particle size. The requirement for particle size distribution should be consistent with those for MDIs as both deliver a mist of product for oral inhalation.

Section/Topic	Line Number(s)	Comments
G. Container Closure Systems	827	We do not believe it is relevant for the Guidance to describe the 'design' in detail and suggest deletion of the examples.
	831 - 832	It is agreed that the design of any metering system should be capable of preventing partial metering, however it is very difficult to design a metering system that is resistant to abuse scenarios that could lead to partial metering. Therefore the following addition to the sentence is proposed " The device should be designed to prevent partial metering of the formulation, **when used in accordance with the patient instructions for use."**
	832 - 833	It is agreed that some form of dose counter or indicator is a benefit to the patient, however stipulating a dose counter in the Guidance document adds a constraint to device designs. A dose indicating mechanism may be more appropriate. To acknowledge this and to recognize unit dose products in this section we suggest the text be modified to " The use of some **type** of dose **indicating** mechanism is encouraged for **multi-dose** products".
	849 - 855	The Guidance should acknowledge that it is not always possible to identify every extractive. The amount of data required for extractives should be based on the available data. For NDAs 12 months of real time data and 6 months of accelerated data are normally submitted in the initial application. There should only be a need to provide additional data if the available data suggest that the level of extractives has not yet reached equilibrium. In this case, we would agree that additional data should be provided.
	855 - 859	There are likely to be differences in the materials of construction of the container closure system between ANDAs and the reference listed drug. Therefore, ANDAs should be required to provide sufficient data to demonstrate that the level of extractives has reached equilibrium. The submission of only 3 months of data may not be sufficient to ensure therapeutic equivalence to the innovator product.
	863 - 868	We suggest that the Guidance state that **relevant,** rather than **complete,** information is required, e.g., there is no added value in providing extensive composition and extraction information for components that are not product contact if they are made of food grade materials.

Section/Topic	Line Number(s)	Comments
G. Container Closure Systems (cont.)	874 - 875	To acknowledge that different firms use distinct systems for identification of components we suggest replacing "item numbers" with "unique identifier".
	884 -889	The relationship between acceptance testing of container closure system components and finished product performance should be determined and specifications related. Parameters controlled to tight specifications for the container closure system may not need to be tested routinely for the finished product.
1. Source, Chemical Composition, and Physical Dimensions	904 - 907	The definition of critical components for the purpose of extractives testing should be defined as product-contact components. There is no added value in measuring and specifying the extractives profile of components that are not product-contact materials if they are made of food grade materials.
	909-911	We welcome the suggestion that samples of the container closure system be submitted as part of the review of these products and request that the Guidance include a specific suggestion regarding the best time to submit the samples, perhaps with the original application, rather than at a later stage in the review process, or on request, as is usually the case with product samples.
2. Control Extraction Studies	926 - 927	We agree that controlled extraction should determine materials that may be extracted under stressed conditions. It is recommended that the solvent used in the controlled extraction studies include one representing the formulation, e.g., an aqueous solution of the same pH, containing any co-solvents present in the formulation.
	930 - 933	The Guidance should acknowledge that it is not always possible to identify and quantify every extractable.
	933 - 947	We suggest these lines be reworded as follows: "Safety concerns will usually be satisfied if the extractives from the components meet food additive regulations and the USP Biological Reactivity test (USP <87> and <88> if appropriate). Otherwise, the evaluation should include appropriate toxicological appraisal of the extractables, which may consist of supportive citations and/or additional in vitro and/or in vivo tests. These data should support acceptance criteria for components in terms of extractable profiles."

Section/Topic	Line Number(s)	Comments
3. Routine Extraction	949 - 962	This section should include wording to allow flexibility in applying acceptance criteria for extractables at the appropriate point in the supply chain. If a correlation can be established between the profile of extractables in the raw polymers and the individual components then it may be appropriate to apply the acceptance criteria to the raw polymer rather than the individual component. It should also be acknowledged that the data may show that routine controls are unnecessary or if appropriate, may be conducted with one solvent selected from the controlled extraction studies.
4. Acceptance Criteria	977 - 979 989 - 995	The performance attributes listed for routine application to every batch of pumps are unnecessary when dimensional controls are already applied to each batch of components. These should be considered for periodic testing to confirm continued compliance by the supplier. This section should include wording to allow flexibility in applying acceptance criteria for extractables at the appropriate point in the supply chain. If a correlation can be established between the profile of extractables in the raw polymers and the individual components then it may be appropriate to apply the acceptance criteria to the raw polymer rather than the individual component. It should also be acknowledged that the data might show that routine controls are unnecessary.
H. Drug Product Stability		
1. Content of Stability Protocol	1008 - 1025	The amount of information recommended by the Draft Guidance to be included in a stability protocol will be very difficult, if not impossible, to consolidate into a manageable document. Acceptance criteria can often be very lengthy, e.g., Spray Content Uniformity, and are already included in the specific drug product specification. We agree that the information should be within a regulatory submission, but would suggest that the Guidance allow flexibility in how an applicant presents the information.

Section/Topic	Line Number(s)	Comments
a. Test Parameters, Acceptance Criteria, and Procedures	1034 - 1046	It is unclear why this section refers to Section III.F as release specifications as this section is titled "Specifications for the Drug Product" which implies release and through life specifications. It would be very helpful if this could be clarified throughout the Guidance.
b. Test Intervals	1048 - 1058	We suggest combining Section b. Test Intervals with Section d. Test Storage Conditions as the two are closely linked. The second sentence should end with ", if appropriate." to acknowledge that intermediate testing will not always occur.
	1051 - 1053	We request that the Guidance be revised to be consistent with the anticipated revisions to ICH Q1A regarding the number of accelerated test points and intermediate test points.
	1053 - 1055	ANDA products will likely differ from the innovator's in several ways, e.g., specifications, suppliers, container and closure materials, and manufacturing process. These differences may adversely affect the performance of the product over the shelf life. Therefore, the same stability requirements should be applied to NDAs and ANDAs, i.e., submission in the application of 12 months data from the long-term condition and 6 months data from the accelerated condition on three batches of drug product. The Guidance in Lines 108 1 – 1083 endorses the need for long term data for these types of drug products in stating that "Due to the complexity of these types of drug products, **accelerated stability studies alone** may not be predictive of the product performance throughout the extrapolated expiration dating period." We request the Draft Guidance be revised to require the same amount of stability data for NDAs and ANDAs.
d. Test Storage Conditions	1070 - 1101	The test conditions should be consistent with ICH Q1A (currently under revision).
	1073	The requirement to perform stability studies on the secondary packaging should only be required where the secondary packaging affords some additional protection, e.g., from light or moisture.

Section/Topic	Line Number(s)	Comments
f. Quality, Purity, and Source of Drug Substance & Excipients	1123 - 1125	We suggest that the requirement to identify the source of excipients should be consistent with lines 227 – 229, that is, only required "for excipients that may have a direct impact on the performance of the drug product."
i. Expiration Dating Period	1147 - 1155	As written, the Draft Guidance does not allow the extrapolation of real time stability data to extend the expiration dating at approval. This is in direct contradiction to ICH Q1A Stability Testing of New Drug Substances and Products which allows limited extrapolation of the real time data beyond the observed range, particularly where accelerated data support this. In addition, the Draft Guidance for Industry Stability Testing of Drug Substance and Drug Products states "The expiration dating period granted in the original application is based on acceptable accelerated, statistical analysis of available long-term data, and other supportive data for an NDA,. . . It is often derived from pilot scale batches of a drug product or from less than full long-term stability data." We request the Guidance incorporate the ICH philosophy and acknowledge that such an extrapolation must be justified in each application.
2. Other Stability Considerations	1159 - 1167	The Draft Guidance provides a very general discussion of when additional stability data should be generated to support changes. As written, this does not provide sponsors with meaningful guidance for change control nor do we believe it is necessary to specify requirements to support changes during development. We recommend this section be deleted from the Guidance.
	1176 - 1179	We request the Agency provide specific reasons why the use of bracketing and matrixing protocols are not, in general, considered appropriate as we are not aware of any scientific evidence that indicates intranasal and oral inhalation products are different from other dosage forms for which FDA accepts bracketing and matrixing. The Guidance should allow the use of bracketing and matrixing protocols for NDAs and sNDAs.

Section/Topic	Line Number(s)	Comments
IV. DRUG PRODUCT CHARACTERIZ-ATION STUDIES	1193 - 1194	Typically, one-time studies need only be performed on a single batch to provide sufficient information and ANDAs should require the same drug product characterization studies as conducted on the reference listed drug.
C. Temperature Cycling	1231 - 1233	The temperature cycling study proposed is technically difficult to achieve and of limited value in evaluating product stability. The thermal inertia associated with the product and the time required for the product to reach equilibrium during each cycle means that products cycled between subfreezing and 40°C three to four times per day will not be exposed to the extremes of the challenge for an acceptable period of each cycle. An alternative with cycling every 12 hours for up to six weeks provides an adequate stress to the product and is readily attainable in practice.
	1238	It may be more appropriate to conduct microbiological challenge studies of the product in its pack during freeze thaw testing (e.g. expose to a suspension of small motile organisms) rather than confirming sterility. Sterility may not be compromised even if the primary pack is damaged, e.g., if the pack was not exposed to microbial contamination.
F. Device Ruggedness	1255 - 1268	It is suggested that the word Ruggedness is replaced with Robustness as it is considered that this is a more accurate description of these studies.
N. Photostability	1342 - 1349	The objectives of photostability testing are unclear. It would be helpful if the Draft Guidance provided additional clarification regarding how the results of photostability testing would be interpreted.

Section/Topic	Line Number(s)	Comments
A. Nasal and Inhalation Spray Drug Products		
2. Labels	1403	The inclusion of a statement to "Shake well before using" should only be if applicable, it might not be required, e.g., for thixotropic suspensions.
4. HOW SUPPLIED Section of the Package Insert	1449 - 1452	The parenthetical note "for. . .reusable devices" contradicts the reference to discarding the unit or container. We believe the guidance is intended to differentiate between discrete packs and refill units, where the device may be reusable. We suggest that this should be reworded as follows: "Additionally, a statement should be included that the unit or container should be discarded when the labeled number of sprays has been dispensed. For reusable devices **with** replacement cartridges or refill units, this labeling should be applied to the unit, not the device. It may be appropriate to label the device with an appropriate replacement or service interval.
B. Inhalation Solutions and Suspensions		
2. Labels	1532	The Draft Guidance should not assume that shaking is required for all products as it depends upon the characteristics of the formulation.
Glossary of Terms	1600 - 1662	The glossary of terms may need to be extended if the concepts of release, stability and regulatory specifications are retained.

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